Original Article

Less is More: We are Administering Too Much Protamine in Cardiac Surgery

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ABSTRACT

Context: Protamine is routinely administered to neutralize the anticlotting effects of heparin, traditionally at a dose of 1 mg for every 100 IU of heparin—a 1:1 ratio protamine sparing effects—but this is based more on experience and practice than literature evidence. The use of Hemostasis Management System (HMS) allows an individualized heparin and protamine titration. This usually results in a decreased protamine dose, thus limiting its side effects, including paradox anticoagulation.

Aims: This study aims to assess how the use of HMS allows to reduction of protamine administration while restoring the basal activated clotting time (ACT) at the end of cardiac surgery.

Settings and Design: A retrospective observational study in a tertiary care university hospital.

Subjects and Methods: We analyzed data from 42 consecutive patients undergoing cardiopulmonary bypass (CPB) for cardiac surgery. For all patients HMS tests were performed before and after CPB, to determine how much heparin was needed to reach target ACT, and how much protamine was needed to reverse it.

Results: At the end of cardiopulmonary bypass, 2.2 ± 0.5 mg/kg of protamine was sufficient to reverse heparin effects. The protamine-to-heparin ratio was 0.56:1 over heparin total dose (a 44% reduction) and 0.84:1 over heparin initial dose (a 16% reduction).

Conclusion: A lower dose of protamine was sufficient to revert heparin effects after cardiopulmonary bypass. While larger studies are needed to confirm these findings and detect differences in clinically relevant outcomes, the administration of a lower protamine dose is endorsed by current guidelines and may help to avoid the detrimental effects of protamine overdose, including paradox bleeding.

Keywords: Anesthesia, cardiac surgery, cardiopulmonary bypass, heparin, hemostasis management system, intensive care, protamine

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INTRODUCTION

Protamine is a simple alkaline protein discovered in the 1870s in the sperm of salmon and is involved in the compact folding and stabilization of DNA. A hundred years later, protamine sulfate was approved for reversing the effects of heparin.[1] Nowadays, it's use is still crucial in cardiac surgery, vascular surgery, and interventional radiology procedures where it is routinely administered to neutralize the anticlotting effects of heparin. In fact, due to its highly cationic state, it can bind heparin forming a stable ion pair, which does not have anticoagulant activity. The ionic complex is then

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removed and broken down by the reticuloendothelial system.[2]

Overdosage of protamine has a paradox anticoagulant effect. This is possibly caused by effects on platelets, inhibition of GPIb-vWF interaction, reduction of thrombin generation, activation of factor V and VII, and factor VIII clotting effect.[3]

Unfractionated heparin for the cardiopulmonary bypass is traditionally administered at a dose of 300 IU/kg with a target activated clotting time (ACT) of 480 seconds(s).[4] Nowadays, more sophisticated systems are available to tailor a heparin dose to the patients' actual needs.

On the other side, protamine use and dosing are controversial: 1 mg of protamine sulfate is administered for every 100 IU of active heparin—a 1:1 ratio—but this is based more on experience and practice than current literature evidence.[3,5,6] Furthermore worldwide, when minor coagulopathy-related bleedings occur, additional protamine is administered in the hope of enhancing hemostasis, even if those bleedings are not related to residual heparin. This behavior may result in additional bleeding and enhanced transfusion requirements.[3] Hemostasis Management System (HMS), when used in addition to the ACT, allows an individualized heparin titration based on a dose-response test. The use of this point-of-care test results in a decreased protamine dose with decreased blood loss and transfusion requirements as well as higher platelet counts at the end of the operation.[7,8]

The aim of the study was to assess if the use of HMS allows reduction of protamine administration while restoring the basal ACT at the end of cardiac surgery.

SUBJECTS AND METHODS

In this study, we analyzed data from 42 consecutive patients undergoing cardiopulmonary bypass (CPB) for cardiac surgery at a tertiary care university hospital between January and June 2017. All patients were adults (>18 years old) and signed written informed consent for scientific data management. Ethical Committee approval was waived according to Italian law.

For all patients, a blood sample was drawn after induction of general anesthesia and HMS test performed by the HMS Plus Hemostasis Management System (Medtronic, Minneapolis, MN, USA). The HMS Plus combines three different tests: it measures actual circulating heparin concentration, assesses patient's response to heparin, and measures ACT based on dosing protocol, patient blood volume, and extracorporeal circuit parameters. The estimated blood volume for each patient—necessary for heparin and protamine dose calculation—was computed according to the method described by Allen *et al*.[9] After induction of anesthesia, a full HMS was run: heparin bolus calculations were performed using Heparin Dose Range cartridges encompassing whole blood heparin concentration ranging from 0.4 to 3.4 U/mL. Three minutes after unfractioned heparin (Epsoclar, Pfizer, New York, NY, USA) administration and 10 min after the onset of CPB, ACT was remeasured using an ACT Plus® System (Medtronic, Minneapolis, MN, USA). If ACT did not reach a value of over 480, additional heparin was administered to reach the target. At the end of CPB, the actual heparin level is measured and the optimum protamine dose calculated. Protamine sulfate (Protamina Meda, Meda Pharma S.p.A, Milan, Italy) was administered accordingly. HMS was performed again after protamine administration to check if any residual circulating heparin was present, and consequently, if any additional protamine was required.

Data on administered heparin and protamine, basal and end of surgery ACT, together with patients' biometrical and demographic data and type of surgery were collected.

Data were stored electronically using a digital Excel spreadsheet (version 16, Microsoft Corporation, Redmond, WA, USA) and presented as medians [interquartile range (IQR) or as means ± standard deviation (SD)]. Means and SDs were applied when the variables were normally distributed, whereas medians and IQRs were applied to non-normally distributed variables.

RESULTS

Included patients were predominantly males (67%) aged 65 ± 10.0 years undergoing different types of cardiac surgery, mostly mitral valve repair (38%) and aortic valve replacement (24%). Eight patients underwent a combined surgery, including combined mitral and tricuspid valve repair (7%), mitral and aortic valve replacement (7%), and combined valvular and coronary surgery (5%) [Table 1].

Patients received 20,286 ± 5,440 IU of heparin—as determined by HMS—to reach target ACT (equivalent to 263 ± 50 UI/kg). All patients reached target ACT upon HMS-driven heparin dose administration. At the end of the surgery, an HMS-driven protamine dose of 2.2 ± 0.5 mg/kg was sufficient to revert heparin. Only in 3 cases, an additional dose of 20 mg of protamine was needed to completely reverse heparin. End-of-surgery ACT was 126 ± 13 s [Table 2].

The administered protamine was a lesser amount to what would have been administered on a standard 1:1 ratio approach, being 44% less over heparin total dose and 16% less over heparin initial dose.

The protamine-to-heparin ratio was reduced by 44% over heparin total dose (ratio 0.56:1) and 16% over heparin initial dose (ratio 0.84:1).

DISCUSSION

A 0.84:1 protamine-to-heparin ratio resulted in sufficient to reverse the effects of heparin after cardiopulmonary bypass. This data is extremely important because sometimes protamine is administered in a 1:1 ratio considering the total dose of administered heparin and, furthermore, a supplement of protamine (25 mg, 50 mg, or even 100 mg) is given during unsatisfactory hemostasis. These behaviors lead to a substantial increase of protamine dose administered to many patients and subsequent protamine-induced paradox hemostasis deficit.

While HMS-driven administration of heparin is widely used and current guidelines on patient blood management for adult cardiac surgery support its use, the correct dosage of protamine is still debated as different guidelines describe different strategies [Table 3].[10-13] To the best of our knowledge, the best guidelines on this topic have been formulated by the European Association for Cardio-Thoracic Surgery and European Association of Cardiothoracic Anesthesiology stating that "It is advised not to exceed a protamine dose in a 1:1 ratio to initial heparin bolus because protamine overdosing might be associated with perioperative bleeding and enhanced transfusion requirements."[12]

Protamine may induce side effects, including hypotension, bradycardia, reduction in myocardial oxygen consumption and cardiac output, increased pulmonary artery pressure and allergic reactions, especially in infertile men, vasectomized patients, or those allergic to fish. The severity of allergic reactions may differ among patients, occurring at rates ranging from 0.28% to 6%.[14-16]

Koster *et al.*[17] was the first to demonstrate that protamine administration based on a 1:1 ratio of the initial heparin dose resulted in overdosing, with longer clotting time and concomitant microvascular bleeding requiring substantial replacement of coagulation factors. Meesters *et al.*[18] revealed that a 1:0.8 ratio over the total heparin dose was significantly associated with reduced postoperative bleeding compared with a dosing ratio of 1:1.3.

Suelzu *et al.*[19] found that a complete reversal of heparin could be effectively achieved with a 1:0.67 ratio over total heparin. They also found that additional administration of protamine (up to 1:1 ratio over total heparin) seemed to induce a prolongation of the clotting time. Impairments of platelet function with the higher ratio of protamine was also demonstrated by previous studies.[20,21] In particular, Gertler and coauthors[20] demonstrated how the addition of protamine worsens platelet function (measured

Table 1: Demographics

	Patients *n*=42
Male sex (*n*, %)	28 (67%)
Age, years (mean±SD)	65±10
Weight, kg (mean±SD)	77±14
Height, cm (mean±SD)	172±9
BMI, kg/m^2 (mean±SD)	25.9±3.8
BSA, m^2 (mean±SD)	1.89±0.20
Type of cardiac surgery (*n*, %)	
Mitral valve repair (*n*, %)	16 (38%)
Aortic valve replacement (*n*, %)	10 (24%)
Mitral valve replacement (*n*, %)	2 (5%)
Coronary artery bypass graft (*n*, %)	3 (7%)
Combined cardiac surgery (*n*, %)	8 (19%)
Other procedures (*n*, %)	3 (7%)

SD: Standard Deviation; BMI: Body Mass Index; BSA: Body Surface Area; ACT: Advanced Clotting Time

Table 2: Heparin and protamine use

	Patients *n*=42
Initial heparin dose, IU (mean±SD)	20,286±5,440
Initial heparin dose, IU/kg (mean±SD)	263±50
Need for additional heparin during CPB, IU (mean±SD)	10,674±5,490
Total heparin dose, IU (mean±SD)	31,095±9,567
Total heparin dose, IU/kg (mean±SD)	402±88
1:1 hypothetical protamine dose (total heparin), mg (mean±SD)	311±97
1:1 hypothetical protamine dose (initial heparin), mg (mean±SD)	203±54
HMS-driven administered protamine dose, mg (mean±SD)	170±59
Difference between hypothetical (initial heparin) and actual protamine dose, mg [(median (IQR)]	33±37
Difference between hypothetical (total heparin) and actual protamine dose, mg [median (IQR)]	141±61
Basal ACT, s (mean±SD)	140±9
End-of-surgery ACT, s (mean±SD)	126±13

IU: International Units; SD: Standard Deviation; CPB: Cardiopulmonary bypass; HMS: Hemostasis Management System; IQR: Interquartile Range; ACT: Advanced Clotting Time

Table 3: Comparison of guidelines statements on protamine administration after cardiopulmonary bypass

Year	Scientific society	Statement
2007[10]	Society of Thoracic Surgeons	It may be reasonable to use either protamine titration or empiric low-dose regimens (e.g., 50% of total heparin dose) to lower the total protamine dose and lower the protamine-to-heparin ratio at the end of CPB, but more evidence is necessary before a higher-class recommendation (class I or IIa) can be made.
2011[11]	Society of Thoracic Surgeons	It is not unreasonable to use either protamine titration or empiric low-dose regimens (e.g., 50% of total heparin dose) to lower the total protamine dose and lower the protamine-heparin ratio at the end of CPB to reduce bleeding and blood transfusion requirements.
2018[12]	European Association for Cardio-Thoracic Surgery and European Association of Cardiothoracic Anesthesiology	It is advised not to exceed a protamine dose in a 1:1 ratio to the initial heparin bolus because protamine overdosing might be associated with perioperative bleeding and enhanced transfusion requirements.
2018[13]	Society of Thoracic Surgeons, Society of Cardiovascular Anesthesiologists, and American Society of Extra Corporeal Technology	It can be beneficial to calculate the protamine reversal dose based on a titration to existing heparin in the blood as this technique has been associated with reduced bleeding and blood transfusion

with aggregometry) and also increase coagulation time (measured with thromboelastography), starting at a 1:1 ratio.

The role of cell salvage of operative blood loss and residual blood from the circuit after CPB in this setting should also be considered. Although salvaged blood after CPB is believed to contain residual heparin, several studies disproved this belief, demonstrating that intraoperative salvaged blood has minimal heparin activity, even in procedures requiring systemic anticoagulation.[22]

While the findings of the present study are relevant, the fact that the small sample size might have had an impact on our results must be taken into consideration. Larger studies are necessary to assess the impact of a lower dose of protamine in cardiac surgery. Also, the quantity of heparin used to obtain systemic anticoagulation in the present study was lower than the traditional dose of 300 IU/kg—as it was dosed by HMS. However, this does not have an impact on the present findings, as the ratio of protamine-to-heparin was calculated over the administered heparin dose.

In conclusion, a protamine-to-heparin ratio of 0.84:1 over initial heparin dose resulted sufficient to revert systemic anticoagulation in the present study. Protamine carries detrimental side effects, and current guidelines[10-13] suggest that its use should be limited. However, while a lower dose than the traditional 1:1 approach is recommended, a new threshold has not been established yet. Further studies should focus on protamine sparing effects on relevant clinical outcomes, including bleeding and blood transfusions.

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Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. Schroeder M, Hogwood J, Gray E, Mulloy B, Hackett AM, Johansen KB. Protamine neutralisation of low molecular weight heparins and their oligosaccharide components. Anal Bioanal Chem 2011;399:763-71.
2. Okajima Y, Kanayama S, Maeda Y, Urano S, Kitani T, Watada M, *et al.* Studies on the neutralizing mechanism of antithrombin activity of heparin by protamine. Thromb Res 1981;24:21-9.
3. Boer C, Meesters MI, Veerhoek D, Vonk ABA. Anticoagulant and side-effects of protamine in cardiac surgery: A narrative review. Br J Anaesth 2018;120:914-27.
4. Jia Z, Tian G, Ren Y, Sun Z, Lu W, Hou X. Pharmacokinetic model of unfractionated heparin during and after cardiopulmonary bypass in cardiac surgery. J Transl Med 2015;13:45.
5. O'Carroll-Kuehn B, Meeran H: Management of coagulation during cardiopulmonary bypass. Contin Educ Anaesth Crit Care Pain 2007;7:195-8.
6. Fromes Y, Daghildjian K, Caumartin L, Fischer M, Rouquette I, Deleuze P, *et al.* A comparison of low vs conventional-dose heparin for minimal cardiopulmonary bypass in coronary artery bypass grafting surgery. Anaesthesia 2011;66:488-92.
7. Noui N, Zogheib E, Walczak K, Werbrouck A, Amar AB, Dupont H, *et al.* Anticoagulation monitoring during extracorporeal circulation with the Hepcon/HMS device. Perfusion 2012;27:214-20.
8. Machovec KA, Jooste EH, Walczak RJ, Homi HM, Jaquiss RD, Lodge AJ, *et al.* A change in anticoagulation monitoring improves safety, reduces transfusion, and reduces costs in infants on cardiopulmonary bypass. Paediatr Anaesth 2015;25:580-6.
9. Allen TH, Peng MT, Chen KP, Huang TF, Chang C, Fang HS. Prediction of blood volume and adiposity in man from body weight and cube of height. Metabolism 1956;5:328-45.
10. Society of Thoracic Surgeons Blood Conservation Guideline Task Force, Ferraris VA, Ferraris SP, Saha SP, Hessel EA 2nd, Haan CK, *et al.* Perioperative blood transfusion and blood conservation in cardiac surgery: The Society of Thoracic Surgeons and The Society of Cardiovascular Anesthesiologists clinical practice guideline. Ann Thorac Surg 2007;83:S27-86.
11. Society of Thoracic Surgeons Blood Conservation Guideline Task Force, Ferraris VA, Brown JR, Despotis GJ, Hammon JW, Reece TB, *et al.* 2011 update to the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists blood conservation clinical practice guidelines. Ann Thorac Surg 2011;91:944-82.
12. Task Force on Patient Blood Management for Adult Cardiac Surgery of the European Association for Cardio-Thoracic

Surgery (EACTS) and the European Association of Cardiothoracic Anaesthesiology (EACTA), Boer C, Meesters MI, Milojevic M, Benedetto U, Bolliger D, *et al*. 2017 EACTS/EACTA Guidelines on patient blood management for adult cardiac surgery. J Cardiothorac Vasc Anesth 2018;32:88-120.
13. Shore-Lesserson L, Baker RA, Ferraris VA, Greilich PE, Fitzgerald D, Roman P, *et al*. The Society of Thoracic Surgeons, The Society of Cardiovascular Anesthesiologists, and The American Society of Extra Corporeal Technology: Clinical practice guidelines-anticoagulation during cardiopulmonary bypass. Ann Thorac Surg 2018;105:650-62.
14. Campbell FW, Goldstein MF, Atkins PC. Management of the patient with protamine hypersensitivity for cardiac surgery. Anesthesiology 1984;61:761-4.
15. Welsby IJ, Newman MF, Phillips-Bute B, Messier RH, Kakkis ED, Stafford-Smith M. Hemodynamic changes after protamine administration: Association with mortality after coronary artery bypass surgery. Anesthesiology 2005;102:308-14.
16. Sokolowska E, Kalaska B, Miklosz J, Mogielnicki A. The toxicology of heparin reversal with protamine: Past, present and future. Expert Opin Drug Metab Toxicol 2016;12:897-909.
17. Koster A, Börgermann J, Gummert J, Rudloff M, Zittermann A, Schirmer U. Protamine overdose and its impact on coagulation, bleeding, and transfusions after cardiopulmonary bypass: Results of a randomized double-blind controlled pilot study. Clin Appl Thromb Hemost 2014;20:290-5.
18. Meesters MI, Veerhoek D, de Jong JR, Boer C. A pharmacokinetic model for protamine dosing after cardiopulmonary bypass. J Cardiothorac Vasc Anesth 2016;30:1190-5.
19. Suelzu S, Cossu A, Pala G, Portoghese M, Columbanu V, Sales G, *et al*. Impact of different dosage of protamine on heparin reversal during off-pump coronary artery bypass: A clinical study. Heart Lung Vessel 2015;7:238-45.
20. Gertler R, Wiesner G, Tassani-Prell P, Braun SL, Martin K. Are the point-of-care diagnostics MULTIPLATE and ROTEM valid in the setting of high concentrations of heparin and its reversal with protamine? J Cardiothorac Vasc Anesth 2011;25:981-6.
21. Carr ME, Carr SL. At high heparin concentrations, protamine concentrations which reverse heparin anticoagulant effects are insufficient to reverse anti-platelet effects. Thrombosis Res 1994;75:617-30.
22. Spain DA, Miller FB, Bergamini TM, Montgomery RC, Richardson JD. Quality assessment of intraoperative blood salvage and autotransfusion. Am Surg 1997;63:1059-63.